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Submission of comments on 'Good manufacturing Practice for Advanced Therapy Medicinal Products' (EMA/…/…)

Comments from:

| Name of organisation or individual |
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| **ANDALUSIAN INITIATIVE FOR ADVANCED THERAPIES (AIAT) AND ITS NETWORK OF 1O GMP FACILITIES** |

This answer is the agreed list of comments from the Andalusian Initiative for Advanced Therapies and its network of 10 GMP facilities. **More than 100 professionals** have contributed to this document, including qualified people, manufacturing managers, quality control and quality assurance managers.

The Andalusian Initiative for Advanced Therapies is a publicly funded organization created in 2008 by the Regional Government of Andalusia to promote R&D&i activitiesin the fields of Cell Therapy and Regenerative Medicine, Clinical Genetics and Genomic Medicine and Nanomedicine, in order to foster both cell and gene technologies and therapies, and to coordinate the provision of regenerative medicine treatments within the Andalusian Public Healthcare System.

So far the Andalusian Initiative for Advanced Therapies has promoted **24 clinical trials** and close to **700 patients** have either participated in those clinical trials or have received an ATMP manufactured in its network of **10 GMP laboratories** (8 authorised by the Spanish Agency for Medicines and Medical Devices) located on the campus of the main university hospitals. The variety of products manufactured in this GMP network includes tissue engineered and cell and gene therapy medicinal products as shown in the table below:



Another important area of activity of the Andalusian Initiative for Advanced Therapies is the provision of different **training programmes** on Good Laboratory Practice, Good Clinical Practice, Good Distribution Practice, Good Pharmacovigilance Practice and Good Manufacturing Practice. In collaboration with the University of Granada, it also offers the following professional training programmes designed with the participation of several members of the **Committee for Advanced Therapies** of the European Medicines Agency:

1. Master Degree in Manufacturing of Advanced Therapy Medicinal Products, specialization as Qualified Person (1,647 hours)
2. Master Degree in Manufacturing of Advanced Therapy Medicinal Products, specialization as Manufacturing Manager (1,559 hours)
3. Master Degree in Manufacturing of Advanced Therapy Medicinal Products, specialization as Quality Control Manager (1,559 hours)
4. Expert Degree in Quality Assurance for Manufacturing of Advanced Therapy Medicinal Products (1,258 hours)

More information related to the Andalusian Initiative for Advanced Therapies can be found on its webpage: [www.juntadeandalucia.es/terapiasavanzadas](http://www.juntadeandalucia.es/terapiasavanzadas)

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | We acknowledge the flexibility introduced in this Guideline for GMP requirements and specially the importance given to the risk-based approach. Irrespectively of the character of this document (to be a standalone document -in which case the detail needs to be far greater or more cross references to current GMP and its annexes are required- or to be an annex of the current GMP) we consider critical its integration in EUDRALEX as well as its inclusion in PIC/S. We are concerned about the potential risk of establishing a double standard for manufacturing ATMPs. For that reason we strongly recommend to the EC the implementation of mechanisms of coordination and collaboration between the EMA and the National Competent Authorities (NCAs) to avoid different interpretations by the inspectors at the different NCAs. To ensure harmonization it should be established that these guidelines shall prevail for ATMPs in case of divergent requirements compared with the current GMP and its annexes. |  |
|  | A glossary of terms and list of abbreviations should be included into the document. |  |
|  | The exceptions for Investigational ATMPS should be summarized at the end of each of the 17 chapters, in order to have a more comprehensive reading within each of the chapters and also to make the differences more feasible. |  |
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1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 167 |  | The term “operators” should be clarified. It should be interpreted as manufactures, developers or others.  **Proposed change (if any):**  To replace operators by a more precise term. |  |
| 237 |  | The importance of assessing different risks for basal media vs. cytokine-containing media and the importance of raw materials being in contact with the cell product is an important issue, but it is suggested to change some words to make the sentence and the examples more clear.  **Proposed change (if any): Suggested text is underlined**  “Additionally, it is important to take into account the level of the risk related to raw materials due to their composition thereof (e.g. higher risk when a culture media contains cytokines vs.low risk with a basal media without cytokines) or the use thereof in the manufacturing process (e.g. higher risk if the raw material comes in contact with the cellular product as a starting material or in the intermediate phases of manufacturing).” |  |
| 268-272 |  | The issue of particulate matter test is of special interest in cell therapy. Visual inspection, that is already problematic for biologics due to subjectivity and dependence on trained personnel, becomes even more problematic for cell therapy products. For developers of cell therapy products, it will be prudent to develop a visual inspection procedure that can detect visible particulates within an opaque liquid in a water/placebo run.  **Proposed change ( if any):**  As particulate matter test in a final product made of a cell suspension is quite problematic, an RBA with appropriate mitigation measures to control the sources of particulate (e.g. classification of the manufacturing area, positive pressure environments to have airflow from clean to less clean areas, airflow patterns and airflow velocity, filtered air with HEPA filters or other, suitable facilities, areas, equipment, and materials, trained personnel, environmental monitoring etc.) can support the possibility to perform a particulate matter test on water/placebo run instead than on the final product. |  |
| 303-313 |  | The requirements for the processing of cell-based medicinal products considered medicinal products in virtue of its indication (according to criteria of same/different essential function) but which are not subject to substantial manipulation should be those established in Directives 2004/23/EC and 2006/86/EC for the processing of cells and tissue for transplant in tissue establishments, not only related to premises and equipment, but in general.  It is believed that, from a risk/benefit analysis, it is disproportionate to ask for the same product characterization, process validation and quality control requirements as in the case of substantially manipulated medicinal products.  Especially disproportionate seems to ask for quality controls according to GMPs in some cases in which the experience has extensively demonstrated the safety of practising quality controls under the requirements established in Directives 2004/23/EC and 2006/86/EC for the processing of cells and tissue for transplant. As an example, the use of non-substantially manipulated cell fractions from bone marrow. They are a group of cell products which have a double classification either as a transplant -when administered for the treatment of patients with hemato-immunologic diseases- or as a medicinal product -when administered for the treatment of diseases different from the formerly mentioned. If the accumulated experience, throughout more than 50 years in the field of hematopoietic progenitor transplantation (HPT), has demonstrated the safety of the quality standards applied to the tissue establishments and the cell and tissue processing for transplant, it does not make sense to increase those manufacturing standards and demand greater quality controls for the same product just because the indication has changed.  And specially, if we take into account that the HPT is generally allogeneic and it is performed in immunosuppressed patients, whilst the cell therapy with the same product for other diseases different from HPT is normally autologous and used in immunocompetent patients. In this regard, see also the comment to lines 284-290.  **Proposed change (if any)**:  To eliminate this paragraph. |  |
| 322-325 |  | The reference to the possibility to manufacture ATMPs upon an adequate RBA in class A with other-than-class B surround has been already well stated in line 296-297. To make compatible to what previously stated it is requested to specify that the surround can be other different than class B.  **Proposed change (if any)**: To substitute the sentence with this one: “For first-in-man trials, production in an open environment may be performed in a critical clean area of grade A in a background clean area other than class B if appropriate...” |  |
| 354-356 |  | We suggest considering some exceptions to make more flexible the requirement of participation in a successful process simulation test prior to participating in routine aseptic manufacturing operations. E.g. it could be possible to participate in a successful process simulation test after or concurrently with validation activities or while manufacturing a master or working cell bank, due to there is no risk for the patient (because none of those products will be directly administered to patients or will be used for manufacturing batches before being carried out all quality controls).  **Proposed change (if any)**: **Suggested text is underlined**  As a general rule, prior to participating in routine aseptic manufacturing operations, personnel should participate in a successful process simulation test (see Section 9.5.3) unless the products are not going to be directly administered to the patients or not before performing all quality controls. |  |
| 370 |  | Eating, drinking, chewing, smoking and applying cosmetics (e.g. hand cream) should not be allowed.  **Proposed change (if any): Suggested text is underlined**  Eating, drinking, chewing, smoking, or applying cosmetics (e.g. hand cream) as well as the storage of food or personal medication should be prohibited in the production and storage area. |  |
| 429-434 |  | In small organisations, where teams are multi-skilled and trained in both QC and production activities, it might be acceptable that the same person is responsible for both roles (production and quality control) with respect not only to different batches but also to different operations / work shifts.  **Proposed change (if any): Suggested text is underlined**  In small organisations, where teams are multi-skilled and trained in both QC and production activities, it is acceptable that the same person is responsible for both roles (production and quality control) with respect to different batches or different operations / work shifts. |  |
| 461 |  | This statement should be expanded to provide possibilities of such as segregation in time and use of closed systems within one area.  **Proposed change (if any):**  Amend this section to include the possibility of segregation in time and use of closed systems for manufacturing ATMPs. |  |
| 540-542 |  | The parameters included in the environmental monitoring programs seem excessive. E.g. temperature and humidity affect the operators comfort but do not directly affect the risk of contamination. Besides this, air pressure differentials, airflow direction, temperature and relative humidity are checked in the annual qualification of the premises.  **Proposed change (if any):**  To substitute should with might: “the environmental monitoring program might include...” |  |
| 546 |  | Monitoring of clean rooms should be performed “in operation”. Usually monitoring in operation is done only for grade A zones.  **Proposed change (if any):**  To substitute “clean rooms” with “grade A zones”. |  |
| 553-555 |  | The degree of environmental control of non-viable particulate and the selection of the monitoring system should be adapted to the specific risks of the product and of the manufacturing process.  **Proposed change (if any): Suggested text is underlined**  “The degree of environmental control of non-viable particulate and the selection of the monitoring system should be adapted to the specific risks of the product contamination and of the manufacturing process”. |  |
| 561 |  | Continuous particle monitoring during manufacturing for all classes is highly questionable. Most importantly is stating that the clean rooms need to be qualified before manufacturing and stability of the room needs to be demonstrated.  **Proposed change (if any):**  It should be clearly written that particle monitoring in class B clean rooms must not be performed for the full duration of critical processing (only for class A). |  |
| 593-596 |  | Monitoring viable particles in closed production system might be impossible (e.g. SEPAX system for bone marrow mononuclear cells selection).  **Proposed change (if any):**  To modify the example as follows: e.g. in a closed production system the monitoring of viable particles might be impossible. |  |
| 601 |  | Error in the heading of the last two columns.  **Proposed change (if any):**  “CFU/plate” in the heading of the last column should be moved to the previous. |  |
| 683-684 |  | When repair or maintenance operations occur in a clean area, it is necessary to clean after this activity but the verification takes more time and in some circumstances it is not possible to wait for the results of the environmental monitoring to restart the production activities.  **Proposed change (if any):** When repair or cleaning operations occur in a clean area, production should not be restarted until ~~it has been verified that~~ the area has been adequately cleaned following validated procedures. |  |
| 735-736 |  | The meaning of “anatomical environment” is not obvious, therefore more clarification is required. |  |
| 759 |  | We consider unnecessary to specify rejection criteria for materials and products. All materials and products not meeting release criteria must be rejected.  **Proposed change (if any):**  To eliminate “and rejection”. |  |
| 796-797 |  | The effectiveness of the blinding procedures should be verified by the sponsor.  **Proposed change (if any):**  To add “by the sponsor”. |  |
| 865-870/889-909/1761-1763 |  | Apparently there is a contradiction between paragraphs 865-870, 889-909 and 1761-1763 related to the time for retention of documents. Some of the data referred in the second paragraph are also part of the batch documentation. We suggest keeping SOPs for 5 years and traceability data for 30 years.  Proposed change (if any): Line 865: substitute batch documentation with SOPs. |  |
| 930-951 |  | The first paragraphs on raw materials, although accurate from the development and authorisation point of view, should not appear here as it is clearly not the responsibilities of the manufacturer "to insure the suitability…”.  Indeed, according to both Annex 1, part IV of Dir. 2001/83 and the EP General Chapter on raw materials, it is the responsibility of the sponsor to identify and set the quality specifications for raw materials (be they critical).  The manufacturer, according to the GMP rules, should apply what has been laid down and authorised in the MA or CTA dossier and in no way should take any responsibility on those raw materials.  **Proposed change (if any):**  To delete lines 931-933 and replace them by lines 944 up to “with the supplier" in line 946.  Continue with the text from lines 934- until "grade are available" in line 938 and go to: "It is the responsibility of the sponsor or marketing authorisation holder to establish quality requirements for raw materials according to the specifications declared in the dossier (CTA or MA)”.  Delete lines 938-951. |  |
| 968-974 |  | It is stated that “critical raw materials in the storage area should be appropriately labelled…. “.  According to GMP, any material stored in a storage area should be well identified and properly labelled. It is also assumed that the label affixed by the supplier will be bearing the requested information. It is proposed to clarify this paragraph.  **Proposed change (if any): Suggested text is underlined**  “Raw materials in the storage area should be appropriately labelled. Upon reception and before storage manufacturer should ensure that the following information appear on the label and should complete them accordingly:”  And continue with lines 970-974. |  |
| 981-986 |  | Regarding starting materials for ATMP, it is reminded that they are not only from human tissues and cells covered by directive 2004/23. They could also be derived from human blood and are covered by Dir. 2002/98.  According to articles 15 and 22 of Regulation 1394/2007, the requirements for donation, testing and storage should be adapted to the regulatory status of the concerned starting material. It is proposed to clarify the paragraph on this aspect, so as not to exclude blood components as possible starting material.  **Proposed change (if any): Suggested text is underlined**  After the first sentence in line 981-982, add the following sentence:”Starting materials from blood component should be in accordance with Directive 2002/98/EC”. |  |
| 1020-1026 |  | In line with previous comments on labelling of raw materials (Lines 968-974), it is proposed to re-organise the paragraph accordingly. For starting materials such as cell, tissues or blood components, they will be delivered with a duly conformed label as imposed by the relevant directive.  **Proposed change (if any): Suggested text is underlined**  Lines 1020-1026 should read: “Starting materials in the storage area should be appropriately labelled. Upon reception and before storage manufacturer should ensure that the label is conforming to the relevant directives. The label should, at least, bear the information relevant for traceability and be completed, where relevant, with the following information:”  And continue with lines 970-974. |  |
| 1030-1042 |  | This paragraph is not clear enough as regards the “initial processing steps of the starting materials”, as there may be some minimal manipulations which could be carried out, by the Tissue or Cell establishments, before considering that the starting material is entering the manufacturing process. As such there is no reason to consider that the starting material is always the immediate sampling/biopsy from the tissue or cell donor/patient. It is the responsibility of the sponsor (or the marketing authorisation holder) to define the “starting material” that will enter the manufacturing process. If there are some processing steps (not substantial manipulations) to be carried out immediately after sampling or prior to shipment to the manufacturing site, this has to described and authorised in the clinical trial authorisation or marketing authorisation dossier. By imposing in lines 1030-1032 that “initial processing steps are manufacturing activities…” seems not to be in line with the flexibility approach.  **Proposed change (if any): Suggested text is underlined**  Lines 1030-1042 should be amended as follows:  Delete Line 1030 and replace by "Depending on the characteristics and definition of the declared starting material for the manufacture process, there may be some initial processing steps on the initial biopsy which can be carried out by the tissues or cell establishment, according to Directive 2004/23. It is accepted that those steps are not performed under GMP environment and it is the overall responsibility of the manufacturer …”. continue on line 1036  Delete lines 1040-1042. |  |
| 1044-1058 |  | The three paragraphs raise several issues for the use of xenogeneic tissues or cells. Most of them have to deal at the development level, as quality issues and should not be discussed as GMP issues. Only the points which are relevant for the GMP conditions should be discussed and clear recommendations made in terms of handling and usage of xenogeneic cells/tissues. It is indeed very likely that the aspect of animal sourcing, or breeding is not of concern for the ATMP manufacturers that are supposed to use only cells or tissues of animal origin, either as raw material or starting material.  **Proposed change (if any): Suggested text is underlined**  Keep the first sentence in line 1044-1046, but delete the next sentences: "The selection of donor animals …. up to founder animals similarly should not be used" and replace by "The selection of donor animals (including source, health status) should conform to the specification and characteristics described and approved in the clinical trial or marketing authorisation dossier”.  Delete line 1053-1058. |  |
| 1098-1099 |  | We consider excessive the requirement: The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored.  **Proposed change (if any):** The storage temperature should be controlled and/or routinely checked. |  |
| 1135 |  | According to the list of responsibility by the person responsible for QC (lines 1830-1846) the list of responsibility by the person responsible for manufacturing should be added.  **Proposed change (if any):**  A list of responsibility by the person responsible for manufacturing should be added. |  |
| 1159-1162 |  | The QP responsibility in case of handling of deviations needs to be mentioned in this paragraph  **Proposed change (if any): Suggested text is underlined**  Please add in Line 1162: “The QP should control that any deviations have been appropriately authorized before releasing the final product”. |  |
| 1186 |  | Typo error.  **Proposed change (if any): Suggested text is underlined**  “The compatibility of labels with storage conditions (e.g. ultra-low storage temperatures, water bath) should be verified.” |  |
| 1204-1205 |  | To have more clarification it should be explained that this paragraph is about the manufacture and qualification/release criteria of the gases used (ID, purity, impurities), as defined in the Ph. Eur. monographs, not about the safety implications of the gases when used, which is explained in the following paragraph or by other process steps.  **Proposed change (if any):**  Gasses that come in to contact with the product during processing should be compliant with the European Pharmacopeia in regard to manufacturing and Qualification and release criteria (ID, Purity, impurities). |  |
| 1206-1207 |  | 0.22 filters are recommended by the majority of incubators’ manufacturers to prevent the entry of particles with the gasses before HEPA-filtering them.  **Proposed change (if any):**  Gasses taken into the aseptic work place or that come into direct contact with the product should be passed through ~~micro-organism retentive~~ a filter to preserve the aseptic conditions.” |  |
| 1216-1217 |  | The current wording may mislead the reader.  **Proposed change (if any):**  Special precautions should be taken to avoid mixing of autologous materials from different donors or other dedicated material. |  |
| 1224 |  | As this paragraph is about prevention of cross-contamination and sterilisation does not prevent cross-contamination this sentence can be deleted.  **Proposed change (if any):**  Delete sentence which starts in line 1224 and ends in line 1226. |  |
| 1244-1245 |  | Not only for autologous but also for allogeneic products the risk for cross-contamination needs to be covered.  **Proposed change (if any):**  Sentence which begins in line 1244 and ends in line 1245 can be deleted. |  |
| 1280-1282 |  | If the batches or products are completely closed and physically separated, the possible risks are evaluated and appropriate measures to avoid mix-ups of materials are implemented, we consider that simultaneous incubation/storage of replication competent vectors/products based on them should be acceptable. To ask for individual equipments (incubators, ultra-freezers, etc,) might be impossible to implement in small GMP facilities.  **Proposed change (if any):**  Delete the sentence. |  |
| 1296-1298 |  | Sometimes it is not necessary to have multiple wrappings when you are going to sterilize the product and that impact in the quality of the product.  **Proposed change (if any):** Sterilisation of articles and materials elsewhere is acceptable provided that there are ~~multiple~~ wrappings, as appropriate to the number of critical stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitization precautions. |  |
| 1320-1321 |  | The sterilisation process (es) applied should be validated and the equipment used to sterilize should include the common materials to use by the manufacturer.  **Proposed change (if any):** change the sentence. “The sterilisation process (es) applied should be validated and the equipment used to sterilize should include the common materials to use by the manufacturer.~~Particular attention should be paid when the adopted sterilization method is not in accordance with the European Pharmacopoeia.~~ |  |
| 1326-1328 |  | The integrity of the sterilised filter must be verified by the filter manufacturer.  **Proposed change (if any):** To eliminate the sentence “The integrity of the sterilised filter should be verified before use and should also be confirmed after use by an appropriate method (e.g. bubble point, diffusive flow or pressure hold test).” |  |
| 1346-1352 |  | The necessary Growth Promotion Test should be mentioned.  **Proposed change (if any):**  In line 1348: Via the growth promotion test the suitability of the media used for the individual media fills needs to be proven. |  |
| 1358-1360 |  | We understand that if the interval between the production of two batches is more than six months the process simulation test can be done just before the manufacturing of the second batch but why it should be necessary to be performed three consecutive runs if the interval between the other aseptic process simulation test is less than one year.  **Proposed change (if any):** **Suggested text is underlined**  Thus, if the interval between the production of two batches is more than six months the process simulation test can be done just before the manufacturing of the second batch ~~(three consecutive runs should be performed)~~. The number of process simulation test that should be performed should be analysed through a risk assessment taking into account the time between the last aseptic process simulation test and the personnel routinely involved in aseptic processes. |  |
| 1381-1382 |  | We consider necessary to specify that we should consult annex 12 when we use ionizing radiation to reduce the bioburden and to sterilize the final product.  **Proposed change (if any): Suggested text is underlined**  Where ionizing radiation is used to reduce bioburden and to sterilize the final product in the manufacturing of the ATMP, Annex 12 to EudraLex, Volume 4, should be consulted for further guidance. |  |
| 1459-1460 |  | It should be distinguished between class A clean rooms and other classes A areas (BSC, isolator). It should be included that for BSCs a full re-qualification (all issues according to DIN EN 12469) should be performed only every 12 months and not every 6 months. The manufacturers of BSC’s recommend the procedure according to DIN EN 12469 once per year. Additional wording on BSC re-qualification is suggested.  **Proposed change (if any): Suggested text is underlined**  “In general, for clean rooms of class A… while for biological safety cabinets (BSC), B, C, and D grades….” |  |
| 1464-1468 |  | It should be made clear that the specifications for premises and equipment should indeed be defined by the manufacturer but this can only be done based on the set of specifications and product/process profile as defined in the authorisation dossier and obviously the "user specifications" set for premises and equipment should also be compatible with the intended process and quality profile to be operated in the premises.  **Proposed change (if any): Suggested text is underlined**  Line 1465 “The user requirement specifications should ensure……. linked to the manufacturing processes, as defined in the MAA**,** are….” |  |
| 1509-1510 |  | The risk of microbial contamination is controlled by microbiological sampling, but endotoxins control is not feasible. Endotoxin contamination is assessed in the product but not in equipments.  **Proposed change (if any):** To eliminate “endotoxin” in the sentence “The risk of microbial ~~and endotoxin~~ contamination should be duly assessed”. |  |
| 1547 |  | Not only the total number of batches manufactured but in addition a time frame should be added. The use of cleaning verification for investigational ATMPs should not be restricted to volumes of production less than three batches. Especially since no time frame is provided within the batches should be produced. The cleaning verification approach should be justified by the manufacturer.  **Proposed change (if any): Suggested text is underlined**  Line 1547:“For investigational ATMPs, cleaning verification is acceptable. In such cases…..” |  |
| 1587-1600 |  | The issue of validation with surrogate materials is well supported and welcome. However, and considering that the limitations evoked in this paragraph were also present at the time of the development (and validation) of the process at pilot scale, in preparation of the authorisation dossier, it is very likely that the "surrogate approach" has also been used at that stage.  It is evident that experience gained during product development and scientific background should as well be taken into account to justify the recourse to surrogate materials already accepted/justified and authorised at the level of development in the CTA.  These two paragraphs give the impression that the issue of "validation with surrogate material" is new and have never been experienced during the development phase. Taking advantage of experience gained during the development to help implementation in commercial GMP facilities is also part of the flexibility approach.  **Proposed change (if any):**  Add some wording around process verification/monitoring during product development with surrogate materials, as justified in the CTA. |  |
| 1650 |  | There is a mistake in the reference 11.3.3 because it doesn´t exist. We think that it refers to 11.3  **Proposed change (if any):** Without the prejudice to **Section 11.3**, instead of Section 11.3.3 |  |
| 1658-1659 |  | We consider very adequate the knowledge, training and experience requirements for QPs introduced in lines 1659-1663. Nevertheless, to maintain exactly the same qualification requirements provided for under article 49 of Directive 2001/83, it seems disproportionate for this type of products. As an example, it does not seem to make sense to maintain the necessity of having theoretical and practical studies on subjects like pharmacognosy.  **Proposed change (if any):**  To eliminate the sentence:” ~~In addition to having the qualification requirements provided for under Article 49 of Directive 1658 2001/83;”~~ |  |
| 1871-1872 |  | Sometimes, when the size of the batch is very small, it might be impossible to meet with this requirement.  **Proposed change (if any):** **Suggested text is underlined**  The retention sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed except when the size of batches is very limited. |  |
| 1886-1888 |  | We consider this requirement (to retain samples of critical raw materials) should be asked for “Authorised ATMP”. In the case of “Investigational ATMPs”, it might be more flexible.  And also, the wording …“retained for two years after the batch release or one year after expiry date of the relevant batch, whichever is the longest” is difficult to realize due to the fact that in autologous setting raw materials are used very often for a bigger amount of individual patient batches over a longer period of time.  We suggest that the time point for retention should be in accordance to shelf life of specific raw materials.  **Proposed change (if any): Suggested text is underlined**  To be added to line 1886: “In Authorised ATMPs samples of critical raw materials should be retained ….” |  |
| 2100-2101 |  | This example could be misleading by understanding that a third party (different from manufacturer and administration site) **that is GMP compliant** could perform reconstitution activities. “That is not GMP-compliant” should be deleted.  **Proposed change (if any):** **Suggested text is underlined**  It is suggested to modify the example as follows: “(i.e. it is not acceptable to have these steps outsourced to a third party).” |  |
| 2116-2203 |  | We consider unreasonable to have the same obligations in the case of automated system for ATMPs that are not subject to substantial manipulation than in the case of automated system for ATMPs that are subject to substantial manipulation. The guidelines should differentiate according to the type of manipulation. Whether the manipulation is not substantial, the obligations which should apply are those established in Directives 2004/23/EC and 2006/86/EC.  **Proposed change (if any):** To add that “In case of ATMPs that are not subject to substantial manipulation: the obligations that should apply are those established in Directives 2004/23/EC and 2006/86/EC” |  |

Please add more rows if needed.